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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,056	11/13/2001	Mark Henry Pausch	01142.0101	6857

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,056	PAUSCH ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6-13,15-26,29,32-35,38-41 and 52-85* is/are pending in the application.

4a) Of the above claim(s) *3,4,6-13,15-25,29,32-35,38-41,53-69,81 and 84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,52,70-80,82,83 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/1/01,11/13/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Notice of Non-compliance, sent 21 January 2004 was sent in error. Upon further consideration, the last Office Action is hereby VACATED. A new Office Action follows:

Detailed Action

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement, sent 1 March 2001, and the Information Disclosure Statement, sent 13 November 2001, have been entered into the record. Applicant's election of Invention IX (Claims 70-80, 82, 83 and 85) in the response of 29 September 2003, is acknowledged. Invention IX encompasses use of a host cell with a mutated G-protein to study a heterologous receptor. Applicants also elected: human α2A adrenergic receptor. In addition, since Claims 26 and 52 encompass use of a cell with a mutation that might read on a host-cell G-protein mutation, Claims 26 and 52 have been included with other claims of Invention IX. Claims 3-13, 15-25, 27, 29, 32-35, 38-41, 53-69, 81 and 84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) and PCT rule 13.2, as being drawn to nonelected inventions, there being no allowable generic or linking claims. Applicant timely traversed the restriction/unity requirement in the response of 22 September 2003. Applicant's traversal is based on prior Restriction requirements, which, for example, placed Claims 13 and 26 in the same inventive group. However, Claims 13 and 26, as amended, read on distinct inventions. Claim 13 encompasses use of a host cell comprising a constitutively-active G-protein coupled receptor, while Claim 26 uses a host cell comprising a modified G-protein.

As per PCT rule 13.2:

"Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression 'special technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

Since claims 13 and 26 involve different special technical features (constitutively-active receptor vs. mutated G-protein, respectively) they are considered separate inventions under PCT rules 13.1. Thus, the holding of lack of unity is deemed to be proper and is made FINAL.

Claims 26, 52, 70-80, 82, 83 and 85 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

Figures

In the Brief Description of the Drawings, Figure 6 is described as comprising *part A* and *part B*. However, the figure itself is not labeled as containing *part A* or *part B*. For clarity, the different parts of Figure 6 must be labeled as described in the Brief Description. See MPEP § 608.01(f) and 37 CFR 1.74.

Appropriate correction is required.

Claim Rejections/Objections

Claim Objections

Claims 26, 52, 70-80, 82, 83 and 85 are objected to for reciting or encompassing non-elected inventions (GPCR's in addition to the α2A adrenergic receptor).

Claims 70, 82, 83 and 85 are objected to for depending from non-elected claims.

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 26, 52, 70-80, 82, 83 and 85 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method of screening for ligands of GPCR's, using a host cell comprising the mutated G-proteins listed in the instant Specification (the 3-5 positive mutations in Table 1 and 2, or Table 3), does not enable use of cells comprising mutations in unspecified cell proteins, or comprising *all* G-protein mutations, including those not yet tested. The Specification is not enabling for use of those mutations that would be ineffective in the disclosed assays and those that would have opposite effects than claimed. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The specification does not reasonably provide enablement for use of mutated G-proteins other than those constructed with oligonucleotides SEQ ID NO: 42-63 and that produce a positive effect on cell growth when tested. The instant Application does not reasonably provide enablement for use of yeast host cells comprising heterologous G-protein coupled receptors and comprising mutated host cell proteins, except for those specified in the instant Specification. As discussed below, and as demonstrated in the instant Specification, most mutations in G-proteins *do not* have positive effects on cell growth. The specification is not enabling for the full scope of the claims, wherein the G-proteins used are implied to be functionally equivalent, and with the assurance that such functionally equivalent G-proteins can be made and tested without undue experimentation and with the assurance that they would have the claimed properties. Nor are claims put forth, in the instant Application, that describe the enabled mutations in adequate detail such that they could be claimed as a genus.

The breadth of claims 26, 52, 70-80, 82, 83 and 85 is too large since the specification fails to provide any guidance on how to produce all encompassed host cell proteins, including all G-protein subunits, and still retain the desired functional response in the heterologous GPCR's. Claims 26, 52, 70-80, 82, 83 and 85 refer to any gene or polypeptide that would result in the desired response, without knowledge of the polynucleotides or polypeptides that would fall within this range. In other words, there is no guidance or working examples, in the instant case, as to what amino acids in the G-protein subunit are necessary to cause an increase in cell responsiveness due to agonist. Alternatively, there is no guidance regarding which deletions in

the G-protein subunit are tolerated while maintaining the claimed functional characteristics. Figure 12 demonstrates that a few mutations in the G-protein subunit do ccause increased responsiveness, but there appears to be no generalizable guidlines that would predict which mutations will yield the desired results.

Mutations in G-proteins may have unexpected negative effects in the cell or organism, no physiological effects at all, or positive physiological effects. Schunkert, et al (1998, Hypertension, 32: 510-513) reports on a G-protein point mutation that results in a severe hypertension in humans. Similar mutations in G-proteins can change their binding characteristics to downstream elements or to other subunits (Stone, et al, 1990, Mol. Cell. Biol. 10(9): 4439-4446; Kang, et al, 1990, Mol. Cell. Biol., 10(6): 2582-2590; Zhang, et al, 2003, Eur. J., Pharmacol., 472: 33-38; Ullah, et al, 2001, Science, 292: 2066-2069). Additionally, splice variants in G-proteins abound, including those that are functionally inferior (see, for example: Wedegaertner, P.B., 2002, BMC Cell Biology, 3: 1-11; Bray, et al, 1986, Proc. Natl. Acad. Sci, 83: 8893-8897). These examples and others illustrate that it is not predictable as to which amino acid mutations or deletions are necessary to produce a G-protein subunit with the claimed characteristics.

In summary, the specification does not provide a description of a repeatable process of producing, nor of working examples of making, all G-protein subunits with the desired characteristics. In addition, the predictability of the art is low with regards to the knowledge of what effects altering the sequence of a G-protein polypeptide would have on the usefulness of that polypeptides in the claimed methods. For this reason, undue experimentation would be

required to determine a structure-function relationship for each possible G-protein polypeptide encompassed by the claims.

Due to the large quantity of experimentation necessary to determine how to use the encompassed G-protein subunits and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to all encompassed subunits, the complex nature of the invention, and the breadth of the claims which fail to recite oligonucleotide SEQ ID NO's--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description.

Claims 26, 52, 70-80, 82, 83 and 85 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 26, 52, 70-80, 82, 83 and 85 are directed to methods of using yeast cells to screen for compounds that have agonist effects on a heterologous GPCR, as measured by a cell growth assay. Dependent claims recite use of a yeast host cell comprising a mutated endogenous protein, or mutated G-protein subunit, especially an alpha subunit.

The specification teaches oligonucleotides used to mutate or delete portions of a G-protein alpha subunit (SEQ ID NO: 42-63), only a few of which have been shown to have a positive effect in the cell-proliferation assay (Figure 12). The specification does not teach

functional or structural characteristics of all encompassed G-protein subunits useful for the claimed methods. The description of one or a few polynucleotides encoding a G-protein polypeptide is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides.

To provide evidence of enablement of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or protein domains that have not been adequately identified. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed G-protein subunit polypeptides, and

therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of use. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the well-described mutations in G-protein subunits described in the Specification, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraph of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26, 52, 70-79, 82, 83 and 85 are rejected under 35 U.S.C. 102(b) as being unpatentable over Price, et al, (1995, Mol. Cell. Biol., 15(11): 6188-6195). Price et al disclose chimeric G-protein subunits in yeast, including alpha subunits, the use of which results in a functionally greater response in heterologous GPCR's, and a positive response in a cell-based growth assay (see the Discussion, page 6193). This reference meets all limitations of claims 26, 52, 70-79, 82, 83 and 85.

Claim 26 is rejected under 35 U.S.C. 102(b) as being unpatentable over Imhof, et al (1996, Mol. Cell. Biol., 16(6): 2594-2605). Imhof, et al disclose an agonist assay in yeast cells comprising a heterologous human progesterone receptor and a mutated endogenous protein - RSP5- that results in an improved functional response of the heterologous receptor (see Figure 2). This reference meets the limitations of claim 26, since claim 26 does not require a positive effect of the mutation on cell growth or proliferation.

Additional References:

Klein, et al, 2000, Proc. Natl. Acad. Sci, 97(7): 3219-3223.

Conclusion: Claims 26, 52, 70-80, 82, 83 and 85 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

SLW

13 September 2004